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(54) Title: LIGHT STABILIZED ANTIMICROBIAL MATERIALS

(57) Abstract: Methods of enhancing the photostabilizing of silver in medical materials are described. More particularly, the methods increase the photostabilization of silver in certain materials comprising hydrophilic, amphoteric and anionic polymers by subjecting the polymers to solutions containing an organic solvent and silver, during or after which one or more agents are added which facilitate the photostabilization of the material.

Light Stabilized Antimicrobial Materials

This application claims the benefit of priority of U.S. Provisional Application No. 60/250,182, filed on November 29, 2000, the entire contents of which are herein incorporated by reference.

5

Field of the Invention

This invention relates to light stabilized antimicrobial materials and methods of preparing antimicrobial polymers for use in wound dressings and medical devices.

Background of the Invention

10 Infection is a problem associated with wounds. Infection can retard wound healing, is traumatic for the patient and can significantly increase treatment costs and time. Consequently there is a need to both prevent and treat infection resulting from wounds or wounds in conjunction with of wound dressings, or the use of other medical devices. Examples of such devices at increased risk include prosthetic devices, implants, or wound dressings used on acute
15 or chronic exudating wounds. This can be achieved by the use of topical antimicrobial agents.

It is known to include antimicrobial agents in materials used in the manufacture of medical devices such as wound dressings, ostomy appliances and others. One such antimicrobial agent is silver which is used in various forms such as salts or other silver compounds and which can be used in the fibers, polymers, textiles and adhesive components
20 used in the fabrication of such devices. A problem with silver-containing materials is that they are typically sensitive to light which causes uncontrolled discoloration of the silver-containing material. Numerous efforts have been made to render such materials photostable, however there is still a need to enhance the photostabilization of silver in certain materials comprising hydrophilic, amphoteric and anionic polymers. This is especially true where such polymers are
25 used in medical devices. Accordingly, improved light stabilized silver-containing polymers and methods for their manufacture have been sought.

U.S. Patent No. 5,770,255 describes methods of forming anti-microbial coatings on the surface of medical devices. The coatings described include metal ions such as silver.

However, this process requires higher than ambient gas pressures and low temperatures, which

are inconvenient and costly. Further this process results in a distinct disadvantage that the coating alters the dimension of the medical device. Such changes in sizes of medical devices such as implants can affect the usefulness of the product. In addition, metal ions present as coatings on the surface of medical devices such as dressings may render the product toxic.

5 U.S. Patent No. 5,326,567 describes methods of making silver-containing compositions for use in medical applications. The compositions contain acrylic polyether polymers such as polyethylene glycol and are coupled with silver nitrate. However, this system is only suitable for use in solutions and is very sensitive to solvent and salt conditions. Further, this system is unlikely to be sufficiently robust to survive sterilization, which is essential for wound
10 dressings. Additionally, this system is unsuccessful when applied to fibrous or hydrocolloid wound dressings.

U.S. Patent No. 3,422,183 discloses the use of ultraviolet irradiated silver fluoride compositions in items such as bandages. The ultraviolet treatment reportedly enhances the activity of the silver, but the problem of photostability is not resolved. Further, this process is
15 problematic with respect to the safety of fluoride compounds in contact with wounds, particularly using concentrations of fluoride compounds that would be required to achieve efficacy.

U.S. Patent No. 4,646,730 discloses light stable polyvinylpyrrolidene/silver sulfadiazine (PVP/SSD) hydrogel dressings, where the gel is formed by utilizing electron beam irradiation
20 to crosslink the PVP. Photostabilization is reportedly provided adding magnesium trisilicate to the gel, and preferably by also adding hydrogen peroxide and/or polyacrylic acid. This process requires specialized equipment to carry out the beam irradiation. Further, this process uses a hydrogel and therefore would be incompatible with other wound dressing types and technologies.

25 WO 00/01973 describes stabilized antimicrobial compositions containing silver for use in wound dressings. The silver is in the form of a complex with a primary, secondary or tertiary amino and the complex is associated to one or more hydrophilic polymers. However, the method of processing limits the type of products that can be produced and also alters the release rate of silver. This process is better adapted to hydrocolloid products which, due to the

adhesive matrix, suffers from low availability of silver. This system is unsuitable for application to water swellable/soluble materials once they have been formulated.

U.S. Patent Nos. 4,906,466 and 5,413,788 disclose antimicrobial compositions suitable for topical use or wound care and which exhibit suppression of light instability. The compositions comprise an antimicrobial silver compound deposited on a physiologically inert oxidic synthetic support material in particulate form, such as titanium oxide. However, the resultant product has been found to be susceptible to darkening due to the reduction of the silver compound to metallic silver. Further, the use of insoluble particulates such as titanium oxide as a support is not desirable in wound healing products because the particulates are considered to be foreign bodies and must be removed.

U.S. Patent No. 4,446,124 relates to the use of ammoniated SSD incorporated into animal tissue to prepare burn dressings. The SSD is incorporated into the tissue by soaking the tissue in an ammoniacal SSD solution or suspension. While the ammonium solution is reported to increase the concentration of silver which can be incorporated into the dressing, photostabilization is not mentioned and is unlikely. Further, this process uses animal tissue as the substrate, which is undesirable for use in wounds.

In accordance with the present invention, a novel method for the preparation of light stabilized silver-containing hydrophilic, amphoteric and anionic polymers is disclosed. This invention describes simple and inexpensive methods for the preparation of such polymers that provide effective and non toxic antimicrobial activity in a water swellable material that can be terminally sterilized.

Summary of the Invention

The present invention is directed to methods of preparing a material which contains one or more hydrophilic, amphoteric or anionic polymers, where the material has antimicrobial activity. Preferably, the material containing the polymer(s) is used in a medical device, a wound dressing, or an ostomy device. Also included in the present invention are polymers and materials prepared by the methods described herein. The present invention is advantageous over the prior art because it is easily applicable to water soluble and/or water swellable materials.

In the inventive method, a solution is prepared comprising an organic solvent and a source of silver. Typically, the source of silver is initially dissolved in water, and a solution is formed by mixing water with the organic solvent. The quantity of silver should be sufficient to provide a desired silver concentration in the material. Appropriate sources of silver include silver salts, such as silver nitrate, silver chloride, silver sulphates, silver lactate, silver bromide, silver acetate silver carbonate, silver iodide, silver citrate, silver laurate, silver deoxycholate, silver salicylate, silver paraaminobenzoate, silver paraaminosalicylate, and/or mixtures thereof. Other appropriate sources of silver include but are not limited to any simple water and/or alcohol soluble silver salt.

Next, the polymer is subjected to the solution for a time that is sufficient to incorporate the desired silver concentration. During or after the period wherein the polymer is subjected to the solution, the polymer is subjected to one or more agents which facilitate the binding of the silver and the polymer together. Suitable agents include ammonia, ammonium salts, thiosulphates, chlorides, and/or peroxides. In one preferred embodiment, the agent is aqueous ammonium chloride.

The resultant material is substantially photostable upon drying of the material. However, the material will dissociate to release the silver if the material is rehydrated.

Detailed Description of the Invention

We have found that it is possible to stabilize silver in polymers which are used in medical-related materials. This gives the advantage that the materials exhibit anti-microbial activity while being less susceptible to photo-degradation or light-sensitivity. Such a light-stabilized medical material is particularly suitable for use in wound dressings, that create a moist wound healing environment particularly those used for moderately or heavily exuding wounds such as chronic or acute wounds. Other medical materials which benefit from the methods described herein include ostomy products, ostomy appliances, or other medical materials that are exposed to potentially infectious agents.

Accordingly, the invention provides methods of preparing a material which contains one or more hydrophilic, amphoteric or anionic polymers, wherein the polymers have antimicrobial activity. Preferably, the material containing the polymer(s) is used in a medical

device, a wound dressing, or an ostomy device. Materials which are particularly adapted for the inventive method include gel-forming fibers such as Aquacel™ (WO 93/12275, WO 94/16746, WO 99/64079, and U.S. Patent No. 5,731,083), or those described in WO 00/01425 or PCT/GB 01/03147; wound dressings containing similar gel-forming fibers behind or
5 overlying a non-continuous or perforated skin-contact layer such as Versiva™ (U.S. Patent No. 5,681,579, WO 97/07758 and WO 00/41661); DuoDerm™ (U.S. Patent No. 4,538,603), DuoDerm CGF™ (U.S. Patent No. 4,551,490 and EP 92 999), or a blend of two or more fibres such as Carboflex™ (WO 95/19795). The present invention well-suited for other materials which contain carboxymethylcellulose. Further, the present invention is advantageous over the
10 prior art because it is easily applicable to water soluble and/or water swellable materials.

Polymers suitable for the present invention include, but are not limited to, polysaccharides or modified polysaccharides, polyvinylpyrrolidone, polyvinyl alcohols, polyvinyl ethers, polyurethanes, polyacrylates, polyacrylamides, collagen, gelatin, or mixtures thereof. In preferred embodiments, the polymers contain carboxymethylcellulose (CMC) such
15 as sodium CMC. In one embodiment, the polymer can be a polysaccharide comprising a carboxymethylcellulose or alginate, or a mixture of carboxymethylcellulose and alginate. In other embodiments, the polymers contain gel-forming fibers comprising sodium CMC, and which can be incorporated into wound dressings such as Aquacel™ (ConvaTec, Skillman, NJ).

In the inventive method, a solution is prepared comprising an organic solvent and a
20 source of silver. The solution should be prepared in a quantity sufficient to provide the desired silver concentration in the resulting product. The polymer is then subjected to the solvent/silver solution so as to incorporate the silver into the polymer. The treated polymer is subjected to one or more agents such that the silver-containing material is made photostable, and further where the silver will thereafter dissociate upon rehydration of the material.

25 The organic solvent can be any known solvent. Examples of appropriate solvents include but are not limited to industrial methylated spirit (IMS, principally ethanol), ethanol, methanol, acetone and isopropyl alcohol.

The source of the silver can be any convenient source. Examples of appropriate sources of silver include silver salts, such as silver nitrate, silver chloride, silver sulphates, silver

lactate, silver bromide, silver acetate silver carbonate, silver iodide, silver citrate, silver laurate, silver deoxycholate, silver salicylate, silver paraaminobenzoate, silver paraaminosalicylate and/or mixtures thereof. Other appropriate sources of silver include but are not limited to any simple water and/or alcohol soluble silver salt.

5 The quantity of silver should be sufficient to provide a desired silver concentration in the material. The final concentration of silver in the material is between about 0.1% and 20% by weight, for example, by weight of the resultant medical dressing. In some embodiments, the concentration of silver is between 0.1 -10%, 1-10%, 10-20%, 5-20%, 5-10% or 0.1-1%. In one preferred embodiment, the final concentration of silver is between about 1 and 5% by weight of
10 the dressing. Preferably, the concentration in the treatment solution is from 0.001 g/g of polymer to 0.2 g/g of polymer, more preferably from 0.01 g/g of polymer to 0.05 g/g of polymer. Preferably, where the source of silver is most facilely initially dissolved in water rather than the neat organic solvent, then added in an appropriate amount to give the desired concentration of silver in the final weight of polymer.

15 Water can be used in the present invention, especially for the purposes of initial solubilization of silver before addition of the silver to the organic solvent. The amount of water should be sufficient such that the silver is adequately dissolved in solution, but not so much to result in hydration of the polymer. While excess amounts of silver can be present in suspension, for example forming a reserve, amounts effective for incorporation into the
20 polymer should be in solution. Such amounts would be easily determinable to those of ordinary skill in the art without undue experimentation. However, the amount of water used is no greater than 50/50 w/w of water to alcohol.

 The length of time that the material is subjected to the solution is a period sufficient to incorporate the desired silver concentration into the polymer. Preferably, the material is
25 subjected to the solution between 1 and 120 minutes. In some embodiments, the incubation time is between 1 and 60 minutes. In other embodiments, the incubation time is between 15 and 45 minutes. In still other embodiments, the incubation time is between 10-60, 10-45, 15-30, 5-15 or 10-20 minutes. Generally, the length of time necessary to subject the material to the solution will depend on the material used and can be easily determined by one of ordinary
30 skill in the art.

Temperatures between 0 to 100°C are appropriate for the present invention but preferably ambient temperatures are used. Different temperatures can be used at different stages within the range stated.

During or after the period wherein the polymer is subjected to the solution, it is
5 subjected to one or more agents which facilitate photostabilization. Suitable agents include ammonia, ammonium salts, thiosulphates, chlorides, and/or peroxides. Preferred agents are ammonium salts such as ammonium chloride, ammonium acetate, ammonium carbonate, ammonium sulphate and metal halides such as sodium, potassium, calcium, magnesium and zinc chlorides. The agents can optionally include mixtures of the above salts. In one preferred
10 embodiment, the agent is added to the treatment mixture as aqueous ammonium salt solution such as ammonium chloride, or is added separately.

The quantity of agent used will depend on the amount of polymer-containing material being prepared and the total volume of solution. Preferably, the agent is present in a concentration between .01 and 50% of the total volume of treatment. In some embodiments,
15 the concentration of agent is between .01-25%, .01-10%, .01-5%, .1-5%, .1-25%, .1-10%, 1-25%, 1-10%, 1-5%, 5-25%, 10-25% or 25-50% of the total volume of treatment.

Once the facilitating agent is applied, treatment is continued for another period of time, e.g., an additional 5-30 minutes, or for a time sufficient to allow photostabilization to occur.

It is also an important aspect of the present invention that the silver is dissolved in an
20 organic solvent to solubilize the silver salt and prevent hydration of the polymer. The silver salt can be added directly to the solvent and stirred gently until dissolved. The photostabilizing step of the process can either follow the silver-loading step or can be initiated during the course of the silver-loading step.

In addition to the articles mentioned herein, the present invention is suitable for use in
25 medical articles such as wound dressings and skin care products.

By the term "loading" herein, is meant, ionic exchange of the cation to the polymer with silver ions.

The term, "photostable" for purposes of the present invention is meant, Controlled colour change to a desired colour with minimal change thereafter.

“Binding” as meant in the present invention, refers to the formation of a photostable compound.

The resultant polymeric material is substantially photostable upon drying. However, the material will dissociate to release the silver if the material is rehydrated.

5 In an exemplary process, an Aquacel™ wound dressing (e.g. 20 g), commercially available from ConvaTec, can be placed in, e.g., 127.5ml of IMS/water (77.5:50 v/v). A silver nitrate solution is prepared, for example, with water and silver nitrate in concentrations to provide the desired final concentrations of silver in the Aquacel™ dressing (e.g., 0.0316 g/mL in water, with 10 mL added to the IMS/water solution). Final concentrations of silver in the
10 dressings can range between 0.1% and 20% by weight of the dressing. Preferably these concentrations are between 1 and 5%. The dressing is subjected to the IMS/silver nitrate for a desired time, e.g., 15-45 minutes. Preferably after this silver treatment, sodium chloride in a concentration between 0.01 and 50% (preferably between 1 and 10%) is added to the IMS/silver nitrate bath and treatment is continued for another period of time, e.g., an additional
15 5-30 minutes.

Aquacel™ wound dressings having between 1 and 5% by dressing weight of silver have been found to be photostable and possess excellent antimicrobial activity. Further, irradiation does not adversely affect such silver dressings.

All publications and references, including but not limited to patents and patent
20 applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth.

What is claimed is:

1. A method of preparing a material comprising a hydrophilic, amphoteric or anionic polymer having antimicrobial activity comprising the steps of
 - 5 a) preparing a solution comprising an organic solvent and a source of silver in a quantity sufficient to provide a desired silver concentration in said material;
 - b) subjecting said polymer to said solution for a time sufficient to incorporate said desired silver concentration into said polymer; and
 - 10 c) subjecting said material, during or after step (b) to one or more agents which facilitate the binding of said silver or said polymer, which is substantially photostable upon drying of said material comprising the hydrophilic, amphoteric or anionic polymer, but which will dissociate to release said silver upon rehydration of said material.
- 15 2. The method of claim 1 wherein said material is used in a medical device.
3. The method of claim 1 wherein said material is used in a wound dressing.
4. The method of claim 1 wherein said material is used in an ostomy device.
- 20 5. The method of claim 1 wherein said source of silver comprises a silver salt.
6. The method of claim 5 wherein said silver salt is selected from the group consisting of silver nitrate, silver chloride, silver sulphates, silver lactate, silver bromide, silver acetate and/or mixtures of said salts.
- 25 7. The method of claim 1 wherein said agent is selected from the group consisting of ammonium salts, thiosulphates, chlorides and peroxides.
8. The method of claim 7 wherein said agent is a metal halide.
- 30

9. The method of claim 7 wherein said ammonium salt is selected from ammonium chloride, ammonium acetate, ammonium carbonate, ammonium sulphate and/or mixtures of said salts.

5 10. The method of claim 1 wherein said polymer comprises a polysaccharide or modified polysaccharide, a polyvinylpyrrolidone, a polyvinyl alcohol, a polyvinyl ether, a polyurethane, a polyacrylate, a polyacrylamide, collagen, or gelatin or mixtures thereof.

11. The method of claim 1 wherein said polysaccharide comprises a
10 carboxymethylcellulose, or alginate or mixtures thereof.

12. The method of claim 1 wherein said organic solvent is selected from the group consisting of industrial methylated spirit, denatured ethanol, methanol, acetone, isopropyl alcohol and ethanol.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/44773

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) : A61K 31/74, 9/70; A61F 13/00 US CL : 424/443, 486, 488, 78.07, 618 According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 424/443, 486, 488, 78.07, 618 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Please See Continuation Sheet																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT																				
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.																		
X --- Y	US 5,326,567 A (CAPELLI) 05 July 1994 (05.07.1994), column 3, lines 7-15, column 7, line 57.	1-8, 12 ----- 9-11																		
Y	WO 84/01721 A1 (BAXTER TRAVENOL LABORATORIES) 10 May 1984 (10.05.1984), page 4, lines 10-end.	1-12																		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.																				
<table border="0"><tr><td>* Special categories of cited documents:</td><td>"T"</td><td>later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td></tr><tr><td>"A" document defining the general state of the art which is not considered to be of particular relevance</td><td>"X"</td><td>document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td></tr><tr><td>"E" earlier application or patent published on or after the international filing date</td><td>"Y"</td><td>document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td></tr><tr><td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td><td>"&"</td><td>document member of the same patent family</td></tr><tr><td>"O" document referring to an oral disclosure, use, exhibition or other means</td><td></td><td></td></tr><tr><td>"P" document published prior to the international filing date but later than the priority date claimed</td><td></td><td></td></tr></table>			* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"E" earlier application or patent published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family	"O" document referring to an oral disclosure, use, exhibition or other means			"P" document published prior to the international filing date but later than the priority date claimed		
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Susan Cog <i>Susan Cog</i> Telephone No. (703)308-0196																		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/44773

Continuation of B. FIELDS SEARCHED Item 3:

USPT

search terms: polymer, polysaccharide, silver, ammonium, antimicrobial